REMARKS

Claims 1, 3-18, and 21-29 are pending. No amendments are made herein. No new matter is entered.

Applicants reserve the right to pursue any canceled subject matter in one or more continuation, divisional, or continuation-in-part applications.

Rejection Under 35 U.S.C. § 103(a)

Claims 1, 3-18 and 21-29 are rejected under 35 U.S.C. § 103 as being unpatentable over Bowman et al. (WO 00/69441, published November 23, 2000) in view of Ishikawa et al. (Biochemical Pharmacology, 1998, vol. 55, pages 1091-1097).

Applicants respectfully traverse the rejection for at least the reasons that 1) the Office Action applies an improper legal standard of obviousness to the facts in the present case; 2) the references fail to teach all of the claimed elements in the dependent claims; 3) the references fail to provide a reasonable expectation of success, and 4) the prior art teaches away from the claimed combination.

The Office Action Applies An Improper Legal Standard To The Facts Of The Present Case

The Examiner has adopted an improper "obvious to try" standard which is inconsistent with post-KSR Federal Circuit rulings in the field of pharmaceuticals.

U.S. case law holds that a proper obviousness inquiry requires four factual inquiries: (a) determining the scope and contents of the prior art; (b) ascertaining the differences between the prior art and the claims in issue; (c) resolving the level of ordinary skill in the pertinent art; and (d) evaluating evidence of secondary consideration. See Graham v. John Deere, 383 U.S. 1, 17-18, 148 USPQ 459, 467 (1966).

Recently, the Supreme Court reviewed the legal standard for obviousness in KSR International Co. v. Teleflex Inc., 127 S. Ct. 1727 (2007). In KSR, the Supreme Court reaffirmed its prior holding that the obviousness analysis requires that "the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved." Id., at 1734 (citing Graham v. John Deere Co. of Kansas City, 383 U.S. 1, 17–18 (1966)). While the Supreme Court found the particular claimed structure in KSR to be obvious, the Court pointedly noted that, consistent with a broad body of patent law, "**a patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art.**" KSR, 127 S. Ct., at 1741 (emphasis added). Rather, to determine whether the differences between the art and the claims would have been obvious, the Court mandated analytical flexibility, leaving intact the Federal Circuit's teaching-suggestion-motivation ("TSM") test, while permitting the "obvious to try" doctrine under certain limited circumstances.

In a series of three recent opinions, the Federal Circuit declined to apply the "obvious to try" standard of KSR in drug cases involving unpredictable solutions, finding the TSM test to be more appropriate. See Takeda Chemical Indus. v. Alphapharm, 492 F.3d 1350 (Fed. Cir. 2007); Ortho–McNeil Pharma. v. Mylan Labs., 520 F.3d 1358 (Fed. Cir. 2008); and Eisai Co. v. Dr. Reddy's Labs. (Fed. Cir. 2008). Specifically, in Takeda, the lack of a finite number of identified and predictable solutions led the Court to state "this case fails to present the type of situation contemplated by the Court when it stated that an invention may be deemed obvious if it was 'obvious to try.'" Takeda, at 1359. Similarly, in Eisai, the Court cautioned that, "[t]o the extent an art is unpredictable, as the chemical arts often are, KSR's focus on these 'identified,

predictable solutions' may present a difficult hurdle because potential solutions are less likely to be genuinely predictable."

While not explicitly set forth, the Office Action clearly applies an "obvious to try" standard for obviousness. For example, the Office Action states that "claims that require no more than the administration of two conventional anti-cancer compositions together in order to treat cancer in a patient set forth prima facie obvious subject matter" (Office Action, p. 5, lines 10-12). The Office Action provides no legal basis for this *per se* rule of obviousness, and indeed, such a *per se* rule fails to determine the scope and content of the prior art (as required under Graham), and is inconsistent with the Federal Circuit's position in KSR. Notably, the Court pointedly stated that, consistent with a broad body of patent law, "**a patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art.**" KSR, 127 S. Ct., at 1741 (emphasis added).

The position of the Office Action appears to be that it is "obvious to try" the random combination of any and all anti-cancer agents, regardless of the teachings of the prior art with respect to those agents. The Office Action takes the position that

> The prior art can be modified or combined to reject claims as prima facie obvious as long as there is a reasonable expectation of success. Use of materials in combination, each of which is known to function for intended purpose, is generally held to be prima facie obvious as the idea of combining them flows logically from their having been individually taught in the prior art

(Office Action, p. 5, lines 3-7). Moreover, the Office Action states that

> Selection of appropriate dosage regimens will vary according to the particular formulation, mode of application, and the particular situs, host and tumor being treated, and such selection would have been well within the purview of the skilled artisan.

(Office Action, p. 4, lines 13-16). Again, the Office Action fails to cite supporting case law for these legal propositions, but is clearly relying on an "obvious to try" legal standard.

Nevertheless, the Office Action's position is legally flawed, in that potential combinations in the field of oncology, as in the Eisai case, are not likely to be genuinely predictable, i.e. the potential combinations and dosage regimens lack a finite number of identified and predictable solutions. The Office Action uses improper hindsight reconstruction to select the exact combination as claimed from among hundreds if not thousands of possible combinations without considering the prior art's teaching away from the actual combination as claimed. As such, the "obvious to try" legal standard is inapplicable, and for reasons as discussed below, the cited references fail to provide a teaching, suggestion, or motivation for arriving at the instant claims with a reasonable expectation of success, when the scope and content of the prior art is properly considered.

The References Fail to Teach All of the Claimed Elements

The Office Action states that

> Selection of appropriate dosage regimens will vary according to the particular formulation, mode of application, and the particular situs, host and tumor being treated, and such selection would have been well within the purview of the skilled artisan.

(Office Action, p. 4, lines 13-16). However, the Office Action fails to provide any teachings with respect to specific elements of various dependent claims. For example, the Office Action fails to provide teachings for the combination of ET-743 and capecitabline, wherein capecitabine is administered in a dosage of about 2000 mg/m^2/day (claim 22); wherein capecitabine is administered in a dosage of about 1600 mg/m^2/day (claim 23); wherein ET-743 is administered in a dose range between 0.9 and 1.2 mg/m^2 (claim 24); wherein ET-743 is administered in a dosage of about 0.9 mg/m^2 (claim 25); wherein ET-743 is administered in a dosage of about 0.9 mg/m^2 on day 1 of a 3 week cycle (claim 26); wherein capecitabine is administered in a dosage of about 1600 mg/m^2/day and ET-743 is administered in a dosage range between 0.9 and 1.2

mg/m^2 (claim 27); or wherein the infusion of ET-743 is carried out on day 1 and the administration of capecitabine from days 2 to 15, every 21 days (claim 28).

As discussed above, it is not legally sufficient to simply dismiss the claimed elements in the dependent claims as being "within the purview of the skilled artisan." Rather, where the "obvious to try" standard is clearly inappropriate, a proper prima facie case would require a teaching, suggestion, or motivation (TSM) from the prior art, and the Office Action fails to provide a TSM analysis for the dependent claims. The Office Action cites various portions of Bowman, but provides no teaching, suggestion, or motivation to take those teachings from Bowman for ET-743 and apply them to the specific combination of ET-743 and capecitabine.

The References Fail To Provide A Reasonable Expectation Of Success

The Examiner provides no technical basis for establishing that one of ordinary skill in the art would have a reasonable expectation of success in arriving at the invention as claimed while maintaining efficacy without inducing unacceptable levels of toxicity.

The Office Action appears to apply In re Aller in holding the present claims obvious. In Aller, the courts have held that differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456 (CCPA 1955) (Claimed process which was performed at a temperature between 40°C and 80°C and an acid concentration between 25% and 70% was held to be prima facie obvious over a reference process which differed from the

claims only in that the reference process was performed at a temperature of 100°C and an acid concentration of 10%.)

The Office Action appears to take the position that the present invention to an anti-cancer combination is arrived at through routine optimization of a result-effective parameter. However, the present invention does not involve a result-effective parameter. Specifically, a particular parameter must first be recognized as a result-effective variable, *i.e.*, a variable which achieves a recognized result, before the determination of the optimum or workable ranges of said variable might be characterized as routine experimentation. In re Antonie, 559 F.2d 618 (CCPA 1977) (The claimed wastewater treatment device had a tank volume to contractor area of 0.12 gal./sq. ft. The prior art did not recognize that treatment capacity is a function of the tank volume to contractor ratio, and therefore the parameter optimized was not recognized in the art to be a result-effective variable). In this case, there is no recognition of the particular combination of ET-743 and capecitabine, and no recognition of which parameters to simultaneously vary to arrive at the claimed regimens of ET-743 and capecitabine while maintaining efficacy and not inducing unacceptable toxicity. Specifically, the Office Action fails to identify the parameter that is being predictably optimized by selecting capecitabine to combine with ET-743 rather than any other of the multitude of anti-cancer agents. Simply put, the Examiner has failed to identify the recognized result that could be predictably arrived at by optimizing a result-effective parameter.

The area of cancer treatment is complex, and many treatments fail during clinical trials. In the case of cancer treatment, there is no basis to conclude that one can routinely and predictably achieve efficacy without inducing unacceptable toxicity. As such, the Office Action provides no rationale why the holding of Aller, which involved the optimization of the

temperature at which a chemical reaction is run, should be applied to the present invention directed to a method of treating cancer.

The Prior Art Teaches Away From the Claimed Combination

The Office Action fails to properly consider the scope and content of the prior art (as required by Graham), and as such, fails to see that the prior art teaches away from the claimed invention.

The invention that is the subject of the present application shows for the first time that a combination of ET-743 and capecitabine can be administered to humans with significant therapeutic efficacy and manageable toxicity. Applicants respectfully submit that this was not obvious with regards to the prior art.

A) Applicants have supplied evidence of actual failure of combinations of capecitabine with another anti-cancer agent compared to success in the instantly claimed combination

Applicants previously presented evidence of the failure of capecitabine as an anti-cancer regimen when combined with the known anti-cancer agent 9-NC. Specifically, when the combination capecitabine and 9-NC was assayed in a Phase I clinical trial, the combination showed no manageable toxicity and minimal antitumoral activity.

Prior to the failure of the combination of capecitabine and 9-NC, it was predicted that the combination would be successful (see Bernaki et al., Ann NY Acad Sci. 2000; 922:293-297; "In vitro antitumor activity of 9-nitro-camptothecin as a single agent and in combination with other antitumor drugs"). Concurrent combination of 9-NC with 5-FU, gemcitabine or paclitaxel suggested that the most synergistic drug combination against human HCT-8 colon cancer cells

was 9-NC with 5-FU. In addition, sequential combination of 9-NC followed by 5-FU, 24h later, appeared to be the most synergistic at high growth inhibitory levels.

Based on the predicted activity, a Phase I dose-escalation study was designed to evaluate the safety and tolerability of the oral combination of 9-NC with capecitabine (Michaelson et al, Cancer, 2003 Jan 1; 97(1): 148-154; "A Phase I study of 9-nitrocamptothecin given concurrently with capecitabine in patients with refractory, metastatic solid tumors"). It was expected that major toxicities would be ameliorated with this oral regime. The investigators noted that, although a better tolerability was expected compared to 5-FU, the combination of 9-NC with capecitabine showed no manageable toxicity and a minimal clinical efficacy; the study's author's noted that "the lack of any objective responses was disappointing, particularly considering the toxicity of this schedule."

As noted by the courts, while absolute certainty is not necessary to establish a reasonable expectation of success, In re O'Farrell, 853 F.2d 894, 903-04, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988), there can be little better evidence negating an expectation of success than actual reports of failure. See, e.g., In re Rinehart, 531 F.2d 1048, 1053-54, 189 USPQ 143, 148-49 (CCPA 1976).

Applicants submit that the evidence of actual failure of anti-cancer combinations with capecitabine must be considered as yet more evidence of the non-obviousness of the instant claims. Moreover, the instant claims fulfill a long-felt need in providing an efficacious combination including capecitabine, where others have tried and failed to arrive at the proper anti-cancer agent to combine with capecitabine, i.e., the instant application shows that the combination of ET-743 and capecitabine resulted in clinical improvement in human patients, and that seven patients (4 sarcoma patients, 1 each of gastric, breast, vaginal, and adenocarcinoma

patients) had stable disease and 1 patient with cholangiocarcinoma had a partial response (see Specification, page 13, last paragraph).

B) The prior art teaches away from the claimed combination

Applicants previously provided evidence that the prior art actually teaches away from the combination of ET-743 with 5-fluorouracil. See Takahashi et al. ("Sequence-dependent Synergistic Cytotoxicity of Ecteinascidin-743 and Paclitaxel in Human Breast Cancer Cell Lines in Vitro and in Vivo," Cancer Research, vol. 62, pages 6909-6915, December 1, 2002, considered by the Examiner in the IDS submitted May 11, 2006 and signed by the Examiner on October 28, 2007). According to Takahashi (page 6914, 2nd column, 2nd paragraph), "[a]nother drug used to treat breast cancer, 5-FU, appears not to be a good partner of ET-743. Moderate antagonism was observed for the combination of ET-743 and 5-FU when ET-743 was administered concomitantly. This antagonistic cytotoxicity was not improved by altering the sequence schedule." Takahashi provides the following data in Figure 1:

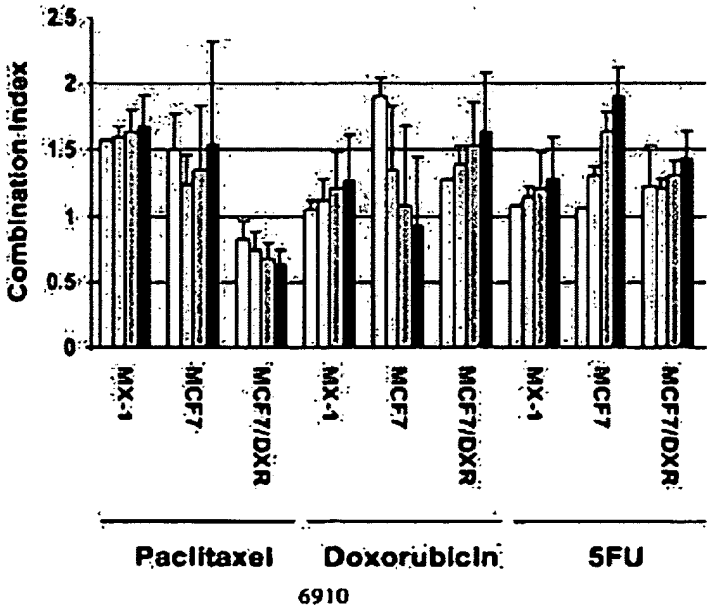

Fig. 1. Concomitant exposures to ET-743 and five other anticancer agents against MX-1, MCF7, and MCF7/DXR cells. After a 96-h incubation, cytotoxicity was determined by the SRB assay. The *CIs* were determined using the CI-isobologram method by Chou and Talalay (11). CI = 1 indicates an additive effect; CI < 1 indicates synergism; and CI > 1 indicates antagonism (see "Materials and Methods"). Data plotted are the *CI* values at 50 (□), 75 (▨), 90 (▨), and 95 (■)% fraction killed and are means of at least three independent experiments; *bars*, SD.

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As can be seen in Figure 1, the combination of ET-743 and 5FU provides a Combination Index (CI) >1 in all three cell lines and under all test conditions (as compared to paclitaxel and doxorubicin, which provide a CI <1 under various conditions). As stated in the legend of Figure 1, a CI > 1 indicates antagonism.

The teaching of Takahashi that ET-743 and 5FU are antagonistic is critical because one of ordinary skill in the art would understand that it is also a teaching away from the combination of ET-743 and capecitabine. Specifically, capecitabine functions as a **prodrug** of 5FU. The advantages of capecitabine (according to Ishikawa) are a result of improved bioavailability compared to 5FU (i.e. capecitabine has better properties when administered orally), but the fact remains that the capecitabine is **converted** into 5FU as the active agent. In other words, if 5FU is ineffective in a cell assay (where bioavailability and delivery issues are not relevant), then it is nonsensical to suggest that capecitabine will remedy the problem. Specifically, the advantages of capecitabine over 5FU as relied upon by the Examiner simply do not exist in the context of cell culture assays. Capecitabine is a prodrug of 5FU, and to have any effect whatsoever, capecitabine must be converted into 5FU. Where the prior art teaches antagonism between ET-743 and 5FU in cell assays, one of ordinary skill in the art would have no reason to use capecitabine.

The Office Action fails to properly consider the evidence teaching away from the present combination. Takahashi (Cancer Research, vol. 62, page 6914) teaches that 5-FU "appears not to be a good partner of ET-743". The Examiner previously disregarded this argument by saying that Ishikawa teaches capecitabine is designed as a prodrug of 5-FU and has certain advantages over 5-FU. However, the advantages of capecitabine over 5-FU (tumor-selective delivery of the active agent) are not relevant to cell assays. In other words, cell assays do not measure

differences in delivery. Ultimately, the active agent from capecitabine is 5-FU, so if the prior art teaches that there is antagonism at the cell assay level, improved delivery will in no way remedy this problem.

Accordingly, for at least the reasons provided above, Applicants submit that the neither of the cited references, whether taken alone or in combination, teach or suggest the claimed invention. Having distinguished the independent claims from the art of record, Applicants submit that the claims dependent therefrom are patentable for at least the same reasons. However, Applicants reserve the right to separately address the patentability of those claims in the future should that become necessary.

CONCLUSION

Based on the foregoing remarks, Applicants respectfully request reconsideration and withdrawal of the rejection of claims and allowance of this application.

AUTHORIZATION

The Commissioner is hereby authorized to charge any additional fees which may be required for consideration of this Amendment to Deposit Account No. **50-3732**, Order No. 13566.105023. In the event that an extension of time is required, or which may be required in addition to that requested in a petition for an extension of time, the Commissioner is requested to grant a petition for that extension of time which is required to make this response timely and is hereby authorized to charge any fee for such an extension of time or credit any overpayment for an extension of time to Deposit Account No. **50-3732**, Order No. 13566.105023.

Respectfully submitted,
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